

A Mixture Tumor Growth Dynamic Model to Describe Differential Patterns of Longitudinal Tumor Response of Advanced Melanoma Patients Treated with Ipilimumab

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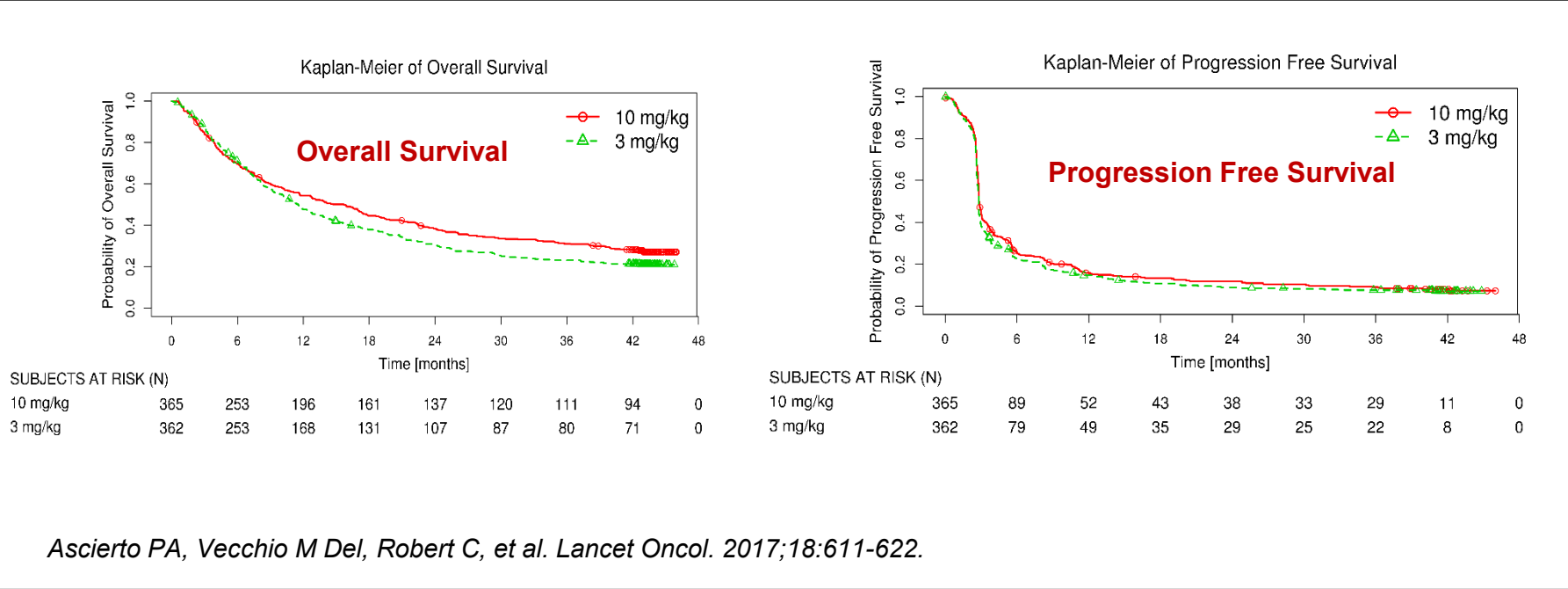
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INTRODUCTION

- Ipilimumab (IPI) was the first immune-checkpoint inhibitor to demonstrate an improvement in overall survival (OS) in advanced melanoma (AdvMel) patients¹, and the approved dosing regimen for AdvMel in the US and EU is 4 doses of 3 mg/kg, given once every 3-weeks (Q3W).
- The benefit-risk of 10 mg/kg vs 3 mg/kg IPI in AdvMel was evaluated in a post-approval randomized phase 3 study (CA184169)², as objective tumor response was higher with 10 mg/kg in a phase 2 dose-ranging study³.
- The overall survival (OS) of AdvMel patients in CA184169 treated with IPI 10 mg/kg Q3W (4 doses) was significantly better than that of the 3 mg/kg dose (hazard ratio 0.84, 95% CI 0.70–0.99; p=0.04). However, Median progression free survival (PFS) were same (2.8 months) in both dose arms [Figure 1] and the objective response rate (ORR) by RECIST criteria, duration of response were also similar in both dose arms.

Figure 1: Kaplan-Meier Plot of OS & PFS by Dose Group



MOTIVATION

- Efforts to characterize the relationship between clinical activity (eg, best overall response rate [ORR]) in early clinical trials and improved efficacy (eg, OS) in pivotal studies is challenging.
- Improvement in ORR is not always associated with improved OS, but longitudinal tumor may enable a more robust characterization of the relationship to OS.
- Characterization of the tumor burden (TB) time-profile may enable identification of one or more features of tumor response that are associated with OS following treatment with immune-checkpoint inhibitors.
- Previously published tumor growth dynamic (TGD) models assumes a uniformed pattern of tumor dynamics that does not account for the heterogeneity of tumor response, and which assumes that ultimately tumor increases in size⁴⁻⁵.
- Current analysis developed mixture TGD model which provided opportunity for better characterization of different pattern of longitudinal tumor size data in compare with the previously published model⁴⁻⁵.

OBJECTIVE

- Characterize the TB time-profile of patients treated with ipilimumab, by a model-based description of longitudinal tumor burden data.
- Utilize the model to assess differences in patterns of TB time-profiles and to identify potential treat/covariate effects on TGD

METHODS

- Both unimodal model and mixture models with 2 or 3 subpopulations were evaluated.
- The TB at a given time (t) could be described by a nonlinear mixed-effect TGD model⁴. Model structure is presented, as below.

$$TB_{i(t)} = TB0_i * e^{-TS_i * t} + TG_i * t + TBss_i$$

Definition of model parameters:

TB_i(t): sum of longest diameters of all target lesions for ith individual at time t;
TB0_i: baseline tumor size;
TG_i: linear tumor growth rate;
TS_i: exponential tumor shrinkage rate constant;
TBss_i: Steady state tumor burden, it is the parameter used in no growth subpopulation (TG fixed to 0) in the mixture models

- Dose effect on TG and baseline lactate dehydrogenase (LDH) effect on TG and TB0 were tested.
- Bayesian information criterion (BIC) was used to guide model selection.

DATA

- CA184169 is a randomized 2-arm, double-blind phase 3 trial. The enrolled AdvMEL patients were stratified by metastasis stage, previous treatment for metastatic melanoma, and Eastern Cooperative Oncology Group performance status.
- The sum of the longest diameters of target lesions was used as a measure of TB.
- The TB time-profiles of AdvMel patients in CA184169 who received ipilimumab, and for whom tumor burden data were available (N=345 for 3 mg/kg; N=344 for 10 mg/kg) were available for TGD analysis.

RESULTS

- The TGD model with 3 subpopulations provided an adequate description of the observed data, and had the lowest BIC value among tested unimodal and mixture models [Figure 2].
- TB0 was higher in subjects in fast tumor growth subpopulation than the other two subpopulations, and TS was similar in both dose arms (3 vs. 10 mg/kg) [Table 1].
- TG of patients in the 10 mg/kg arm was ~50% slower than that of patients in the 3 mg/kg arm (0.015 vs. 0.021 cm/week).
- Subjects with higher baseline LDH appears to be associated with higher tumor growth rate and higher baseline tumor size.

Figure 2: Individual Predicted % Change in Tumor Size vs. Time, by Treatment and Model Assigned Subpopulation

Based on the pattern of tumor growth dynamics (e.g., TS: tumor shrinkage and TG: progression), patients were categorized into 3 subpopulation by the mixture TGD modeling

- No growth:** Subj. only have tumor shrinkage, maintain at constant TBss
- Intermediate:** Subj. has initial shrinkage and then tumor progression
- Fast:** Subj. have fast tumor progression

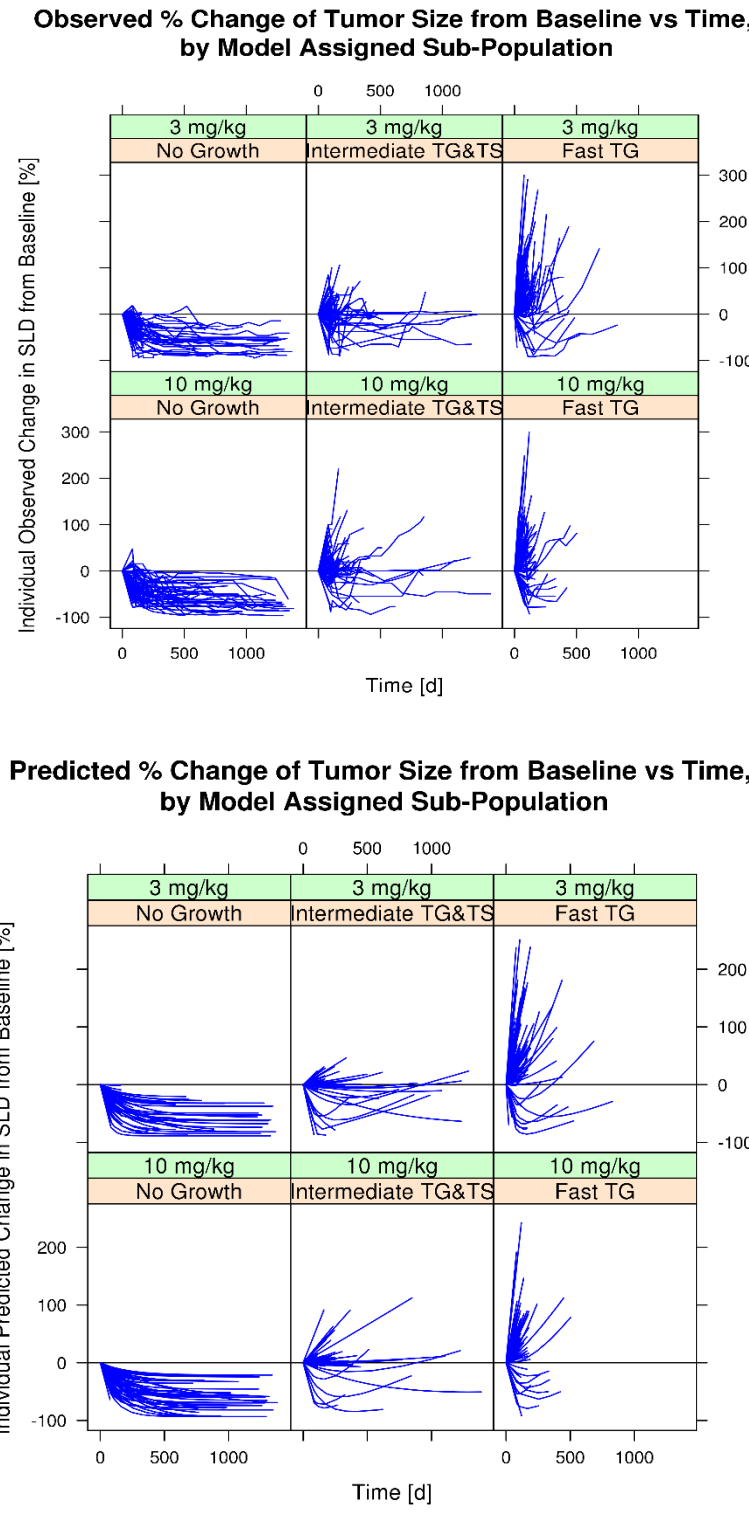


Table 1: TGD Model Parameters Estimates

Name [Units]	Estimate	95% Confidence Interval
Structural Model Parameters		
TB0 [cm] (No growth)	2.47	2.36 - 2.59
TS [1/day] (No growth)	0.0440	0.0426 - 0.0453
TBss (No growth)	1.76	1.60 - 1.92
TB0 P3 [cm] (Intermediate)	5.88	5.80 - 5.96
TG P3 [cm/week] (Intermediate)	0.0482	0.0481 - 0.0484
TS P3 [1/week] (Intermediate)	0.00322	0.00310 - 0.00334
TB0 [cm] (Fast)	10.3	10.3 - 10.3
TG [cm/week] (Fast)	0.562	0.522 - 0.602
TS [1/week] (Fast)	0.00370	0.00338 - 0.00401
P1**	1.19	1.14 - 1.24
P2**	0.947	0.895 - 0.998
LDH effect on TB0	0.869	0.841 - 0.897
LDH effect on TG	0.631	0.610 - 0.653
Dose (10 mg/kg) effect on TG	-0.684	-0.707 - -0.661
Inter-Individual Variability Model Parameters*		
ω ² TB0	0.533 (0.730)	0.457 - 0.610
ω ² TG (Fast)	0.384 (0.620)	0.264 - 0.504
ω ² TS (Fast)	4.12 (2.03)	2.72 - 5.52
ω ² TS (No growth)	0.404 (0.636)	0.174 - 0.635
ω ² TBss (No growth)	1.38 (1.17)	0.933 - 1.83
ω ² TG (Intermediate)	0.189 (0.435)	-0.0324 - 0.411
ω ² TS (Intermediate)	3.21 (1.79)	1.85 - 4.57
ωTG (Fast): ωTS (Fast)	-1.12 (-0.890)	-1.47 - -0.768
ωTG (Intermediate): ωTS (Intermediate)	-0.00721 (-0.00925)	-0.377 - 0.362

*Estimate values in parentheses are standard deviation for estimated variances and correlation for estimated covariances
**Percentage of subject in Fast, no growth, and intermediate sub-population are: 38%, 30% and 32%.

RESULTS (continued)

Figure 3: Model Evaluation: Individual Observed vs. Predicted at Week 12

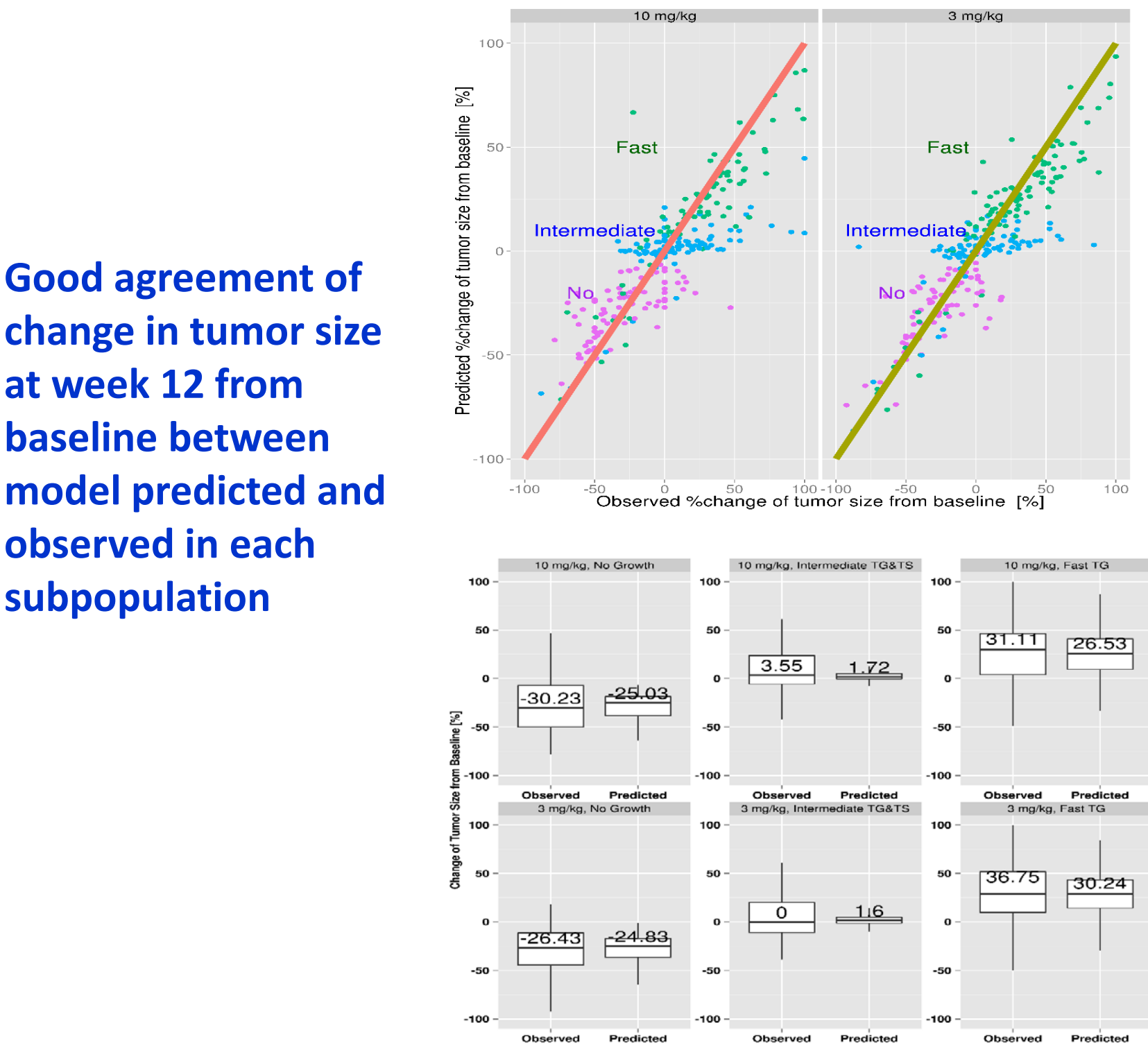


Figure 4: Model Application: Distribution of TGD Parameter Estimates in Each Model Assigned Subpopulation

The 3 subpopulations determined by the mixture model identified subjects with qualitatively different tumor growth dynamics, as evidenced by differences in the distributions of TG and TS values

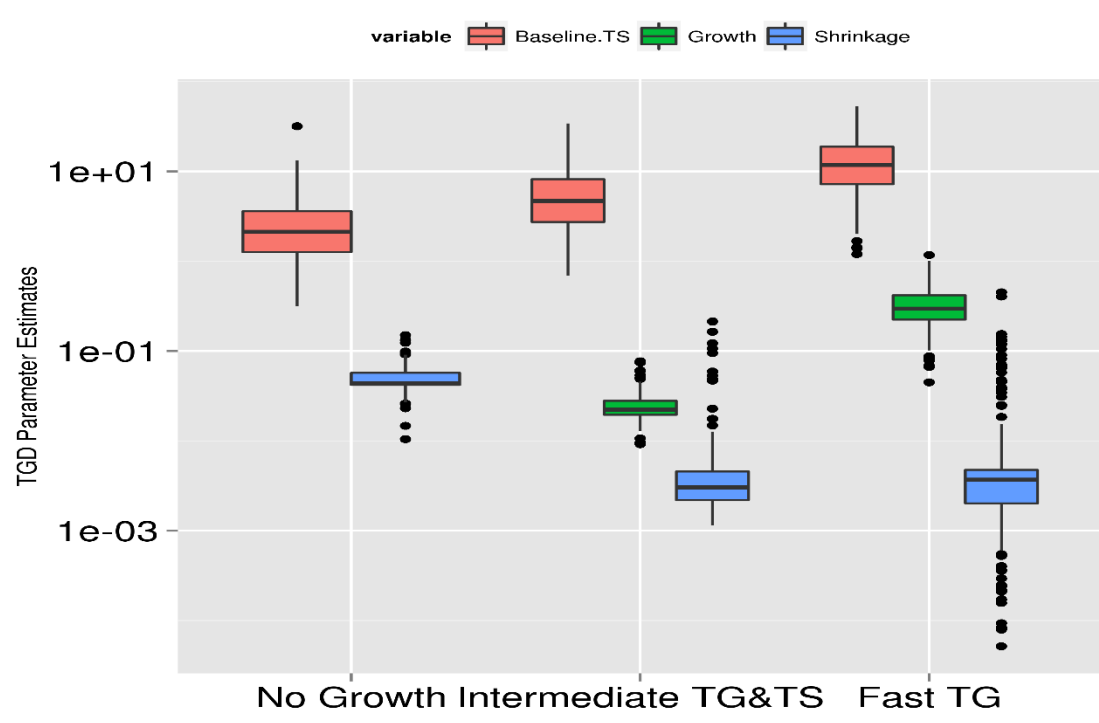


Table 2: Categorization of Subpopulation by Dose Group

Subjects with 10 mg/kg ipilimumab administration appear to have high fractions of no growth and lower fraction of fast growth relative to that in 3 mg/kg.

Treatment Arm	% Subj in No growth	% Subj in Intermediate TG & TS	% Subj in Fast TG
3 mg/kg (N=344)	26.45	26.45	47.09
10 mg/kg (N=345)	31.3	30.14	38.55

CONCLUSIONS

- The TB time profiles of AdvMel patients treated with IPI were adequately described by a mixture TGD model, with 3-subpopulations (fast, intermediate, and no-growth).
- The proportion of subjects achieving durable responses were higher, and tumor progression rate was lower in patients who received 10 mg/kg relative to those received 3 mg/kg.

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